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Terminal Disclaimer filed ✓

TITLE: Methods and compositions for enhanced delivery of bioactive molecules

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INVENTOR-INFORMATION:

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US-CL-CURRENT: 424/501; 424/423, 424/489, 424/502, 514/772.3

CLAIMS:

What is claimed is:

1. A pharmaceutical formulation for controlled release of a bioactive molecule, the formulation comprising a biodegradable polymer in combination with a conjugate of a bioactive molecule and a hydrophilic polymer, wherein the formulation is in the form of microparticles or nanoparticles encapsulating the conjugate, the formulation having a lower initial burst than a formulation of the bioactive molecule without being conjugated to the hydrophilic polymer.

2. The pharmaceutical formulation of claim 1 wherein the bioactive molecule and the hydrophilic polymer are covalently conjugated.

3. The pharmaceutical formulation of claim 1 wherein the biodegradable polymer is selected from the group consisting of polyhydroxy acids, polylactic acids, polyglycolic acids, and copolymers thereof.

4. The pharmaceutical formulation of claim 3 wherein the biodegradable polymer is selected from the group consisting of polyanhydrides, polyorthoesters, and polysaccharide polymers.

5. The pharmaceutical formulation of claim 1 wherein the hydrophilic polymer is selected from the group consisting of polyethylene glycol, polypropylene glycol, copolymers of polyethylene glycol and polypropylene glycol, and linear and branched derivatives of polyethylene glycol and polyethylene glycol/polypropylene glycol copolymers.

6. The pharmaceutical formulation of claim 1 wherein said bioactive molecule is selected from the group consisting of .alpha.-interferon, .beta.-

interferon. .gamma.-interferon, erythropoietins, granulocyte colony stimulating factor, granulocyte macrophage colony stimulating factor, interleukin 1, interleukin 2, interleukin 3, interleukin 12, asparaginase, adenosine deaminase, insulin, glucagon-like peptides, ACTH, glucagon, somatostatin, somatostatin, rhymosin, parathyroid hormone, pigmentary hormones, somatomedin, leuteinizing hormone, chorionic gonadotropin, hypothalmic releasing factors, antidiuretic hormones, thyroid stimulating hormone, endorphins, enkephalins, biphalin, prolactin, monoclonal antibodies, polyclonal antibodies, antisense oligonucleotides, aptamers, therapeutic genes, heparin, low molecular weight heparin and small bioactive molecules.

7. A method for controlled systemic delivery of bioactive molecules to a subject comprising administering to the subject a formulation comprising a biodegradable polymer in combination with a conjugate of a bioactive molecule and a hydrophilic polymer, wherein the formulation is in the form of microparticles or nanoparticles encapsulating the conjugate, the formulation having a lower initial burst than a formulation of the bioactive molecule without being conjugated to the hydrophilic polymer.

8. The method of claim 7 wherein the composition is administered orally.

9. The method of claim 7 wherein the composition is administered by inhalation or mucosal delivery.

10. The method of claim 7 wherein the composition is administered by injection.

11. The method of claim 10 wherein the injection is subcutaneous or intramuscular.

12. The method of claim 7 wherein the bioactive molecule and the hydrophilic polymer are covalently conjugated.

13. The method of claim 7 wherein the biodegradable polymer is selected from the group consisting of polyhydroxy acids, polylactic acids, polyglycolic acids, and copolymers thereof.

14. The method of claim 7, wherein the hydrophilic polymer is selected from the group consisting of polyethylene glycol, polypropylene glycol, copolymers of polyethylene glycol and polypropylene glycol, and linear and branched derivatives of polyethylene glycol and polyethylene glycol/polypropylene glycol copolymers.

15. The method of claim 7 wherein said bioactive molecule is selected from the group consisting of .alpha.-interferon, .beta.-interferon, .gamma.-interferon, erythropoietins, granulocyte colony stimulating factor, granulocyte macrophage colony stimulating factor, interleukin 1, interleukin 2, interleukin 3, interleukin 12, asparaginase, adenosine deaminase, insulin, glucagon-like peptides, ACTH, glucagon, somatostatin, somatotropin, thymosin, parathyroid hormone, pigmentary hormones, somatomedin, leuteinizing hormone, chorionic gonadotropin, hypothalmic releasing factors, antidiuretic hormones, thyroid stimulating hormone, endorphins, enkephalins, biphalin, prolactin, monoclonal antibodies, polyclonal antibodies, antisense oligonucleotides, aptamers, therapeutic genes, heparin, low molecular weight heparin and small bioactive molecules.

16. A method for increasing bioavailability of a bioactive molecule,

comprising conjugating the bioactive molecule with a hydrophilic polymer, formulating the conjugated bioactive molecule with a biodegradable polymer, wherein the biodegradable polymer is in the form of microparticles or nanoparticles encapsulating the conjugated bioactive molecule, and administering the resulting formulation to a subject, the formulation having a lower initial burst than a formulation of the bioactive molecule without being conjugated to the hydrophilic polymer.

17. The method of claim 16 wherein the formulation is administered orally.

18. The method of claim 16 wherein the bioactive molecule and the hydrophilic polymer are covalently conjugated.

19. The method of claim 16 wherein the biodegradable polymer is selected from the group consisting of polyhydroxy acids, polylactic acids, polyglycolic acids, and copolymers thereof.

20. The method of claim 16 wherein the hydrophilic polymer is selected from the group consisting of polyethylene glycol, polypropylene glycol, copolymers of polyethylene glycol and polypropylene glycol, and linear and branched derivatives of polyethylene glycol and polyethylene glycol/polypropylene glycol copolymers.

21. The method of claim 16, wherein said bioactive molecule is selected from the group consisting of .alpha.-interferon, .beta.-interferon, .gamma.-interferon, erythropoietins, granulocyte colony stimulating factor, granulocyte macrophage colony stimulating factor, interleukin 1, interleukin 2, interleukin 3, interleukin 12, asparaginase, adenosine deaminase, insulin, glucagon-like peptides, ACTH, glucagon, somatostatin, somatotropin, thymosin, parathyroid hormone, pigmentary hormones, somatomedin, leuteinizing hormone, chorionic gonadotropin, hypothalmic releasing factors, antidiuretic hormones, thyroid stimulating hormone, endorphins, enkephalins, biphalin, prolactin, monoclonal antibodies, polyclonal antibodies, antisense oligonucleotides, aptamers, therapeutic genes, heparin, low molecular weight heparin and small bioactive molecules.

22. A method for reducing immunogenicity of a bioactive molecule, comprising conjugating the bioactive molecule with a hydrophilic polymer, formulating the conjugated bioactive molecule with a biodegradable polymer, and administering the resulting formulation to a subject, wherein the formulation is in the form of microparticles or nanoparticles encapsulating the conjugate, the formulation having a lower initial burst than a formulation of the bioactive molecule without being conjugated to the hydrophilic polymer.

23. The method of claim 22 wherein the formulation is administered orally.

24. The method of claim 22 wherein the bioactive molecule and the hydrophilic polymer are covalently conjugated.

25. The method of claim 22 wherein the biodegradable polymer is selected from the group consisting of polyhydroxy acids, polylactic acids, polyglycolic acids, and copolymers thereof.

26. The method of claim 22 wherein the hydrophilic polymer is selected from the group consisting of polyethylene glycol, polypropylene glycol, copolymers of polyethylene glycol and polypropylene glycol, and linear and branched derivatives of polyethylene glycol or polyethylene glycol/polypropylene glycol

copolymers.

27. The method of claim 22, wherein said bioactive molecule is selected from the group consisting of .alpha.-interferon, .beta.-interferon, .gamma.-interferon, erythropoietins, granulocyte colony stimulating factor, granulocyte macrophage colony stimulating factor, interleukin 1, interleukin 2, interleukin 3, interleukin, 12, asparaginase, adenosine deaminase, insulin, glucagon-like peptides, ACTH, glucagon, somatostatin, somatotropin, thymosin, parathyroid hormone, pigmentary hormones, somatomedin, leuteinizing hormone, chorionic gonadotropin, hypothalmic releasing factors, antidiuretic hormones, thyroid stimulating hormone, endorphins, enkephalins, biphalin, prolactin, monoclonal antibodies, polyclonal antibodies, antisense oligonucleotides, aptamers, therapeutic genes, heparin, low molecular weight heparin and small bioactive molecules.

28. A method for producing a pharmaceutical formulation for controlled release of a bioactive molecule, the method comprising: dissolving (a) a biodegradable polymer and (b) a conjugate of a bioactive molecule and a hydrophilic polymer in a solvent to form a monophase, and forming microparticles or nanoparticles comprising the biodegradable polymer encapsulating the conjugate.

29. The formulation of claim 1, wherein the biodegradable polymer comprises a copolymer of polylactic acid and polyglycolic acid and the hydrophilic polymer comprises polyethylene glycol.

30. The formulation of claim 1, wherein the bioactive molecule is selected from the group consisting of a protein, a peptide and a small molecule.

31. The formulation of claim 1, wherein the bioactive molecule comprises insulin.

32. A pharmaceutical formulation for controlled release of a bioactive molecule, the formulation comprising a biodegradable polymer in combination with a conjugate of a bioactive molecule and a hydrophilic polymer, wherein the biodegradable polymer comprises a derivatized biodegradable polymer containing hydrophilic and hydrophobic regions.

33. The formulation of claim 32, wherein the hydrophilic region comprises polyethylene glycol.

34. The formulation of claim 32, wherein the bioactive molecule comprises insulin.

35. The formulation of claim 32, wherein die hydrophobic region comprises a polymer selected from the group consisting of polyhydroxy acids, polylactic acids, polyglycolic acids, and copolymers thereof.

36. The formulation of claim 1, wherein the hydrophilic polymer comprises polyethylene glycol.

37. A pharmaceutical formulation for controlled release of a bioactive molecule, the formulation comprising a biodegradable polymer in combination with a conjugate of a bioactive molecule and a hydrophilic polymer, wherein the conjugate of the hydrophilic polymer and a bioactive agent is predominantly a single species.

38. The formulation of claim 37, wherein the hydrophilic polymer comprises

polyethylene glycol.

39. The formulation of claim 38, wherein the polyethylene glycol is linked to the bioactive molecule predominantly at a single site on the bioactive molecule.

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